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(71) Applicant: **ANGIOMEDICS II, INC.**
11700 Twenty-Sixth Avenue North
Plymouth, MN 55441 (US)

(72) Inventor: **Clarke, Richard H.**
55 Collier Road,
P.O. Box 354
Scituate, MA 02066 (US)

(74) Representative: **Strehl Schübel-Hopf Groening & Partner**
Maximilianstrasse 54
D-80538 München (DE)

(54) Inhibition of restenosis by ultraviolet radiation.

(57) Restenosis following angioplasty can be inhibited by reducing the proliferation of smooth muscle cells in the blood vessel walls at an angioplasty site, and such reduction in cell proliferation can be accomplished by an apparatus which irradiates the angioplasty site with radiation in the ultraviolet (UV) wavelength range. The ultraviolet radiation is preferably delivered via an optical fiber or other waveguide incorporated, for example, into a percutaneous catheter. In operation, the ultraviolet radiation kills smooth muscle cells at the site, thereby reducing the risk of restenosis, while minimising damage to surrounding tissue.

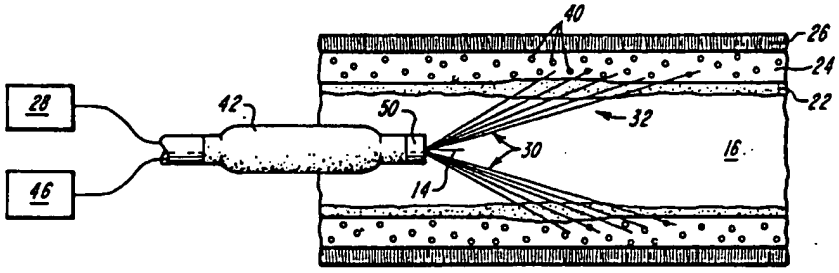

FIG. 3B

EP 0 629 380 A1

Background of the Invention

The technical field of this invention is surgical instruments and, in particular, systems for inhibiting restenosis associated with angioplasty.

Atherosclerosis is a disease which causes thickening and hardening of the arteries, characterized by lesions of raised fibrous plaque formed within the arterial lumen. Atherosclerotic plaque is commonly treated by means of angioplasty through the use of a balloon catheter. Balloon angioplasty involves passing a small, balloon-tipped catheter percutaneously into an artery and up to the region of obstruction. The balloon is then inflated to dilate the area of obstruction. Other devices, such as atherosclerectomy instruments which remove obstructions by peeling or shaving plaque from the artery wall, are also utilized in the treatment of atherosclerosis. More recently, laser systems have been proposed for performing angioplasty. In laser angioplasty, a catheter carrying a fiber optic waveguide is passed through a blood vessel, positioned near an obstruction, and then activated to decompose the plaque with laser radiation.

At present, over 200,000 angioplasty procedures are performed each year in the United States. Unfortunately, restenosis, or closure of the blood vessel following angioplasty, is a common occurrence following all types of such surgery. Approximately 30% of segments dilated by means of balloon catheter will develop significant restenosis, with peak incidence occurring between 2 and 3 months after angioplasty. Similar restenosis rates accompany laser angioplasty. When restenosis occurs, further coronary difficulties can result including strokes, arrhythmia, infarcts and even death.

Evidence suggests that intimal hyperplasia or proliferation of smooth muscle cells is a major factor in restenosis. Proliferation of smooth muscle cells is very common in patients after angioplasty, whether or not restenosis occurs. Medial smooth muscle cells, a main component of the arterial wall, proliferate in response to any injury to the arterial wall. Smooth muscle cells enter their growth cycle between 2 and 3 days after injury, and the majority of smooth muscle cells will cease to proliferate within 7 days. The total number of smooth muscle cells in the intima reaches a peak about two weeks after injury and remains constant for up to one year, suggesting that a reduction of the number of smooth muscle cells injured during angioplasty will reduce the likelihood of subsequent restenosis. See, generally, Liu et al., "Restenosis After Coronary Angioplasty, Potential Biologic Determinants and Role of Intimal Hyperplasia," Vol. 79, Circulation, pp. 1374-1387 (1989).

At present, efforts to prevent restenosis typically consists of drug therapy or modification of angioplasty techniques. Drug therapy is primarily directed toward the control of restenosis through the use of antiplatelet agents, antiproliferative agents, or antimigratory agents. The goal of drug therapy is to reduce smooth muscle cell proliferation by attacking the smooth muscle cells directly, or by affecting processes that promote smooth muscle cell proliferation. Unfortunately, most of the drugs under investigation are unproven, with unknown efficiency and side effects.

An alternative approach to reduce restenosis is to modify the techniques used in performing angioplasty. Until recently, angioplasty was performed by passing a small, balloon-tipped catheter percutaneously to an obstruction site and then inflating the balloon to dilate the area of obstruction. In balloon angioplasty, the outward compression of the balloon stresses the vessel walls, often resulting in cracking or tearing of the wall and injury to the smooth muscle cells. This injury, in turn, increases the risk of restenosis. One method to reduce restenosis resulting from balloon angioplasty is to heat the balloon during dilation to "seal" the injured vessel wall. See, for example, U.S. Pat. No. 4,754,752 issued to Ginsberg et al. on July 5, 1988; and European Patent Application Pub. No. A-0 182 689 published 28 May 1986.

Modified forms of laser angioplasty have also been proposed to remove atherosclerotic obstructions. Up until recently, researchers in laser angioplasty primarily have relied upon continuous wave (CW) lasers. Such lasers, while sufficient to ablate an obstruction, can also substantially cause thermal injury to vessel walls adjacent to the obstruction. Recently, high energy excimer lasers and other pulsed laser sources, which possess high peak intensity levels and very rapid pulse rates, have been found to destroy the target obstruction while minimizing the thermal injury to surrounding tissue. See, for example, European Patent Application Pub. No. A-0 152 766 published 28 August 1985 and European Patent Application Pub. No. A-0 341 943 published 15 November 1989.

Nonetheless, even with these less traumatic procedures, restenosis continues to be a significant factor compromising the effectiveness of angioplasty.

There exists a need for better methods and devices for preventing restenosis after angioplasty. A system which could perform angioplasty, while reducing the likelihood of smooth muscle cell proliferation in the vicinity of the angioplasty site, would satisfy a significant need in the art.

Summary of the Invention

Restenosis following angioplasty can be inhibited by reducing the proliferation of smooth muscle cells in the blood vessel walls at an angioplasty site, and such reduction in cell proliferation can be accomplished by irradiating the angioplasty site with the appropriate radiation in the ultraviolet (UV) wavelength range. The ultraviolet radiation is preferably delivered via an optical fiber or other waveguide incorporated, for example, into a percutaneous catheter. In operation, the ultraviolet radiation kills smooth muscle cells at the site, thereby reducing the risk of restenosis, while minimizing damage to surrounding tissue.

Various UV radiation sources can be used in accordance with the present invention to deliver restenosis-preventive therapy, including both laser and non-coherent radiation sources. Either pulsed or continuous wave ("CW") lasers can be used, and the lasant medium can be gaseous, liquid or solid state. One preferred laser source is a pulsed excimer laser, such as a KrF laser. Alternatively, rare earth-doped solid state lasers, ruby lasers and Nd:YAG lasers can be operated in conjunction with frequency modification means to produce an output beam at the appropriate UV wavelength In another alternative, a UV flash lamp can be employed.

The UV radiation source produces an output beam having a wavelength less than about 280 nanometers. The therapeutic UV radiation useful in the present invention ranges from 280 nanometers down to 240 nanometers (due to the limited transmission efficiency of glass fibers at lower wavelengths). In one preferred embodiment, a laser system is disclosed which operates at about 266 nanometers to maximize the cytotoxic effect of the radiation. Other useful UV radiation sources include, for example, Argon ion lasers emitting UV light at about 257 nanometers and KrF excimer lasers emitting light at about 248 nanometers.

The invention can be practiced with a low energy radiation source. The term "low energy" is used herein to describe both laser and non-coherent radiation systems having an energy output of less than 5 millijoules per pulse.

The term "high energy" is used herein to describe lasers which have an energy output of more than 5 millijoules per pulse or which generate peak powers on the order of 100 kilowatts per square centimeter or greater.

In one embodiment of the invention, at least one optical fiber for transmission of UV radiation is incorporated into a conventional balloon angioplasty device and operated to deliver therapeutical UV radiation to the angioplasty site either at the same time the balloon is inflated, or shortly before or after inflation. In one preferred method, the balloon is first inflated to displace the vessel-obstructing plaque or lesion, and then the balloon is retracted to permit irradiation of the site by one of the optical waveguides incorporated into the catheter. In one illustrated embodiment, the balloon catheter has a diffusive tip through which the therapeutic UV laser radiation of the invention is delivered.

In another embodiment of the invention, at least one optical waveguide for transmission of UV radiation can be incorporated into an laser angioplasty device as an adjunct to the delivery of ablative laser radiation. Thus, a single catheter preferably can carry two bundles of optical fibers, one bundle serving to deliver ablative radiation (e.g., from a high energy, pulsed, excimer laser) and the other bundle carrying the UV radiation to kill a portion of the cells in the vicinity of the ablation site which would otherwise proliferate.

In this embodiment, the ablative and therapeutic radiation can be provided by two or more lasers operating in tandem, one laser source being used to deliver ablative laser radiation, and another laser source then employed to inhibit restenosis. In one preferred embodiment, separate optical waveguides can be used to deliver the ablative and therapeutic laser radiation, and two controllers are provided, one for each laser source, to allow them to operate independently. Alternatively, the ablative and therapeutic radiation can multiplexed and delivered via the same waveguide The ablative laser radiation source can be any form of laser deemed appropriate for the particular application involved. In another alternative, a tunable laser delivering radiation at two or more wavelengths can be used and may be preferred for particular applications.

In another aspect of the invention, novel UV radiation sources are disclosed herein which overcome the problems of low transmissivity and low damage thresholds in fused silica or glass fibers by doping the fiber with a lasant such as Neodymium. The optical fiber is then pumped by energy from an optical pump source and acts as an amplifier to produce a full strength laser output beam at its distal end. High intensity pulsed radiation can be achieved by introducing a low power laser pulse into the proximal end of the fiber. Short wavelength visible and/or ultraviolet radiation can be obtained by disposing one or more frequency-modifying elements at the distal end of the instrument.

In one illustrated embodiment, a laser having an output beam wavelength of about 1064 nanometers, such as a common Nd:YAG laser, can be used in conjunction with two doubling crystals to yield a radiation output of about 266 nanometers. A grouping of six to eight fibers delivering such radiation can be used to

provide the laser power necessary for both ablation of plaque and treatment of the site to reduce the likelihood of restenosis.

Novel catheter systems are also disclosed herein. Such catheter systems are useful in the performance of either balloon angioplasty or laser angioplasty and are preferably equipped with at least one optical waveguide for delivery of the UV radiation therapy, which can be, for example, an optical fiber having about a 200 micron diameter core. The catheter tip can also contain focusing optics or diffusive elements for use in directing the radiation emitted from the catheter within an artery.

Brief Description of the Drawings

FIG. 1 is a schematic perspective view of a combined balloon and laser therapy catheter for performing angioplasty and reducing the likelihood of restenosis;

FIG. 2 is a view of the distal end of the catheter of FIG. 1;

FIGS. 3A-3C are schematic cross-sectional illustrations of a system incorporating the catheter of FIG. 1 in use to dilate a blood vessel and prevent restenosis;

FIG. 4 is a schematic perspective view of an alternative catheter for performing angioplasty and reducing the likelihood of restenosis;

FIG. 5 is a view of the distal end of the catheter of FIG. 4;

FIGS. 6A-6C are schematic cross-sectional illustrations of a system incorporating the catheter of FIG. 4 in use to dilate a blood vessel and prevent restenosis; and

FIG. 7 is a schematic illustration of a laser device useful in the present invention.

Detailed Description

In FIG. 1, a combined balloon and laser therapy catheter 10 is shown, including inflatable balloon section 42 and a guide wire 14. Also disposed within the catheter are a plurality of optical fibers 54 for delivery of ultraviolet radiation. The catheter can also include a radio-opague tip 50. In FIG. 2, the distal end 12 of the catheter of FIG. 1 is shown in more detail, including an exemplary disposition of six optical fibers 54 about a central guide wire 14.

The use of the catheter system 10 is schematically illustrated in FIGS. 3A-3C. In use, the guide wire 14 is first introduced into the obstructed blood vessel and used to guide the catheter 10 into position adjacent to the plaque or lesion (e.g., under radiographic control). As shown in FIG. 3A, the balloon section 42 is then inflated to form a balloon 44 which applies pressure against the obstruction 20, thereby dilating the obstructed region of the blood vessel 16. Inflation and deflation of the balloon 44 are controlled by a balloon controller 46.

In FIG. 3B, the balloon section 42 is deflated and retracted so that the distal tip of the catheter can be positioned to deliver UV radiation therapy to the angioplasty site 32. A therapeutical laser 28 can then be activated to deliver UV radiation 30 which will kill a major portion of the smooth muscle cells 40 within the media 24 of the blood vessel wall without damaging either the inner endothelium layer 22 or the outer adventitia 26 of the blood vessel.

As shown in FIG. 3C, the end result of the operation is a substantially lessened obstruction with few, if any, smooth muscle cells remaining in the angioplasty site to proliferate and cause restenosis.

In FIGS. 4 and 5, an alternative catheter configuration 10A for performing both angioplasty and reducing the likelihood of restenosis is shown, including a guide wire 14 and two laser radiation delivery systems 76 and 78. The first laser delivery system 76 provides therapeutic UV radiation to inhibit restenosis. The second laser delivery system 78 operates to provide ablative laser radiation to remove obstructions in a blood vessel by photodecomposition. Like the system of FIG. 1, the catheter of FIG. 4 can also include a radio-opaque tip 50 to aid in positioning the catheter within a blood vessel under radiographic control.

As shown in more detail in FIG. 5, the distal end of 12A of the catheter can include both the therapeutic UV radiation delivery system 76 and the ablative laser radiation delivery system 78. Multiple optical fibers 54 for UV radiation therapy are encased in a sleeve 66 which is positioned on one side of the guide wire to provide the UV therapy system. A second sleeve 67, encasing another set of optical fibers 68 for laser ablation, is positioned on the other side of the guide wire 14.

The catheter can further include a flushing port 72 for the introduction of saline at the site and/or a suction port 74 for clearing the site of fluids during laser operations. The optical waveguides 68 may be of any type appropriate to deliver the ablative laser radiation required for a particular application. For example, the optical waveguide 68 can be optical fibers connected to an ablative radiation source such as a XeCl excimer laser operating in a pulsed mode at about 308 nanometers.

The use of the catheter system 10A is schematically illustrated in FIGS. 6A-6C. As shown, the catheter and guide wire can be introduced into a blood vessel 16. The walls of the blood vessels are characterized as having an inner endothelium layer 22, a media populated by smooth muscle cells 24 and an outer adventitia 26. In atherosclerotic disease, the endothelium 22 is interrupted by lesions of raised fibers plaque 20. In use, the catheter 10A is positioned next to the obstruction 20 and the ablative radiation source 38 is activated to provide a radiation beam 36 which removes the plaque by photodecomposition. Next, the therapeutic UV radiation source 28 is activated to provide a second beam of radiation 30 which is directed to the smooth muscle cells 40 within the blood vessel media 28 at the angioplasty site 32.

Following the therapeutic UV radiation, the catheter can be withdrawn as shown in FIG. 6C, and few smooth muscle cells will remain within the area of the angioplasty injury. By killing a major portion of the smooth muscle cells, the risk of restenosis is again decreased.

As noted above, the therapeutic UV radiation can be provided by a variety of sources, including non-coherent UV light sources and excimer laser sources (e.g., a KrF excimer laser operating at 248 nanometers).

In FIG. 7, an alternative laser device 70 is shown which can be used in the present invention to provide the therapeutic UV radiation. In the system 70, an output beam from a laser source 48, such as Nd:YAG laser with an output radiation having a wavelength of about 1064 nanometers is introduced via coupler 56 into an optical fiber 54 which is preferably a rare earth-doped silica fiber (e.g. a Neodymium-doped optical fiber). As the radiation from laser source 48 is introduced into the optical fiber 54, the fiber is also optically pumped by an optical pump source 52 (e.g., a laser diode having an output radiation wavelength of about 808 nanometers, likewise coupled to the fiber 54 by coupler 56). The doped optical fiber thus acts a laser amplifier.

At the distal end of fiber 54, the system is terminated in two frequency-multiplying crystals 60 and 62. The first crystal 60 is a frequency-doubling optical element, such as a potassium dihydrogen phosphate (KDP) crystal, and the second crystal 62 is also a frequency-doubling optical element, such as a barium boron oxide (BBO) crystal. Focusing optics 64, such as a grated refractive index ("GRIN") lens, can be included at the output end of the optical fiber 54. With the system as described, laser radiation of a wavelength of about 266 nanometers is produced.

In the laser device 70 of Fig. 7, the pulsed Nd:YAG laser is chosen for its capability to operate as a rapidly pulsed laser and for its availability at low cost. In particular applications it may be preferred to employ pulsed energy sources other than a Nd:YAG laser. The pulsed laser medium can be gaseous, liquid or solid-state. Rare earth-doped solid state lasers, ruby lasers, alexandrite lasers, carbon dioxide lasers and excimer lasers are all examples of lasers that can be operated in pulsed mode and used as pulse-triggering elements in the present invention.

The laser device 70 is particularly adapted for use within a catheter. In one embodiment, a plurality of optical fibers of the type described herein can be used to provide the needed energy for performing either laser surgery or restenosis preventive therapy. The laser surgical systems of the present invention preferably have an output energy ranging from about 50 to to about 100 millijoules per pulse. For a non-ablative, therapeutic application, the systems can be operated at lower output energies, for example, from about 100 microjoules to about 10 millijoules. Other output energies can be employed as needed for particular applications. Likewise, the number of delivery fibers can be varied to adjust the total system output. Moreover, the laser device of Fig. 7 can be incorporated into other surgical tools, such as laser scalpels and/or endoscopes.

The utility of UV radiation in reducing the proliferation of vascular smooth muscle cells has been further demonstrated by experiments In one set of experiments using cultured cells, the A10 rat embryonic thoracic aorta cell line was obtained from the American Type Culture Collection. This clonal, smooth muscle line was derived from the thoracic aorta of DDIX embryonic rats. The cells possess many of the characteristics of end-stage smooth muscle cells; they produce spontaneous action potential at the stationery phase of growth and exhibit an increase in activity of the enzymes mykinase and creatine phosphokinase.

The cell line was propagated in DMEM medium supplemented with 10% fetal bovine serum and glutamine. These cells were plated on well tissue culture plates. After incubation for three to four days, cells in expotential growth were irradiated using laser radiation of various wavelengths. All of the experiments were run at a laser repetition rate of 10 Hz. The area of cell wall exposed was approximately 9.62 cm^2. The results are detailed in Table 1 below.

TABLE 1

Results of Laser Irradiation of Smooth Muscle Cells			
Laser Wavelength	Energy/Pulse	Exposure Time	Surviving Fraction
control	--	--	1.05
control	--	--	0.95
266 nm	10 mj	1 min	0.00916
266 nm	9.6 mj	15 sec	0.0358
266 nm	9.9-1.1 mj	1 min	0.114
355 nm	10.2 mj	1 min	1.12
1064 nm	>10 mj	1 min	1.03
266 + 532 + 1064	>10 mj	1 min	<0.001
532 + 1064	>10 mj	1 min	1.08

These results clearly demonstrate the efficacy of UV radiation in killing aortic smooth muscle cells. Cell cultures exposed to as little as 15 seconds of UV radiation exhibited survival rates below 1 percent.

Claims

1. A phototherapeutic apparatus comprising
   a catheter (10) adapted for insertion inside a blood vessel (16) and location adjacent to a treatment site within the vessel,
   characterised in that the catheter (10) includes non-ablative, low-power UV irradiation means disposed within the catheter for irradiating the treatment site (32) with UV radiation having a wavelength ranging from 240 to 280 nm with an energy level below 5 mJ per pulse sufficient to kill a portion of smooth muscle cells (40) forming the blood vessel (16) in the vicinity of the treatment site, the UV radiation means delivering therapeutical radiation to the treatment site without ablation lesions or damage to the surrounding tissue of the blood vessel, thereby reducing susceptibility to restenosis due to blood vessel cell proliferation.

2. The apparatus of claim 1 wherein the UV irradiation means further includes an optical diffuser at the distal end to diffuse the radiation.

3. The apparatus of claim 1 wherein the UV irradiation means further includes a low power laser (28) emitting UV radiation.

4. The apparatus of claim 3 wherein the laser (28) delivers a radiation beam having a wavelength of about 248 to about 268 nm.

5. The apparatus of claim 1 wherein the UV irradiation means further includes a UV flash lamp emitting UV radiation.

6. The apparatus of claim 3, 4 or 5 wherein the UV irradiation means further comprises at least one optical waveguide (76) disposed within the catheter (10).

7. The apparatus of claim 1 wherein the means for performing angioplasty further includes inflatable means (42, 44).

8. The apparatus of claim 1 wherein the means for performing angioplasty includes an optical waveguide (78) for delivery of ablative laser radiation to plaque at the treatment site (32).

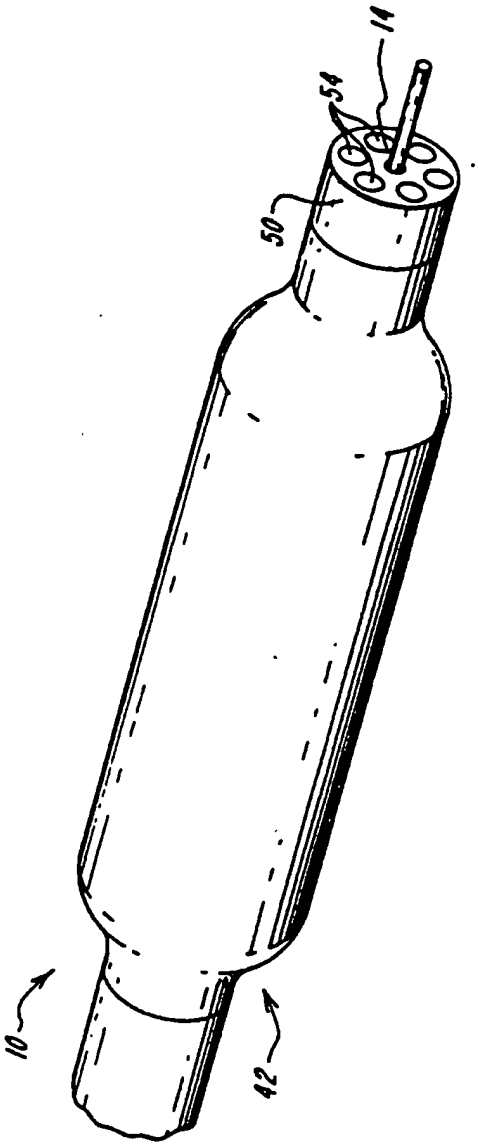

FIG. 1

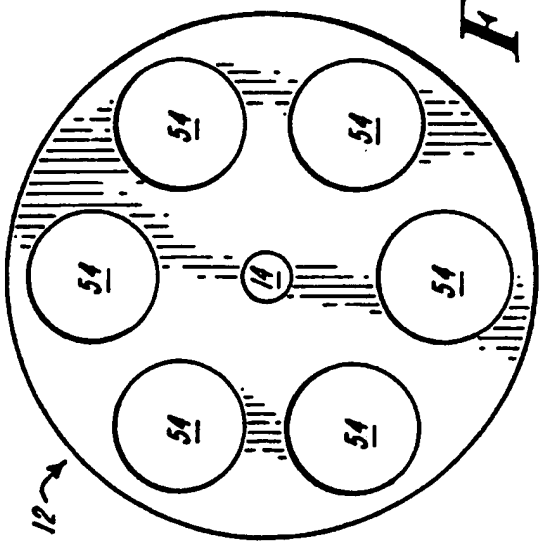

FIG. 2

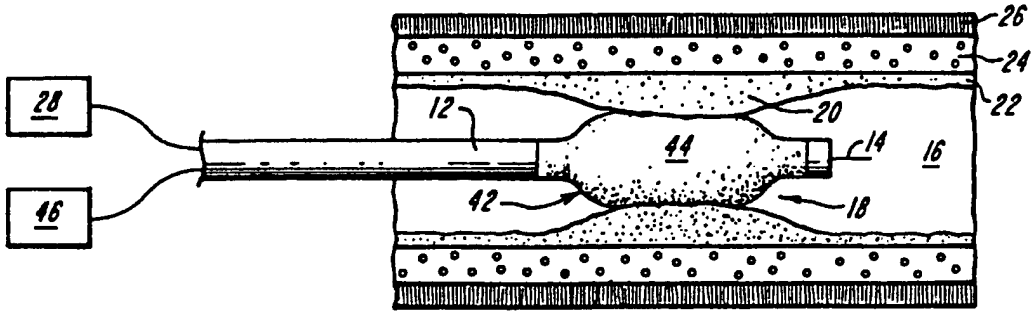

FIG. 3A

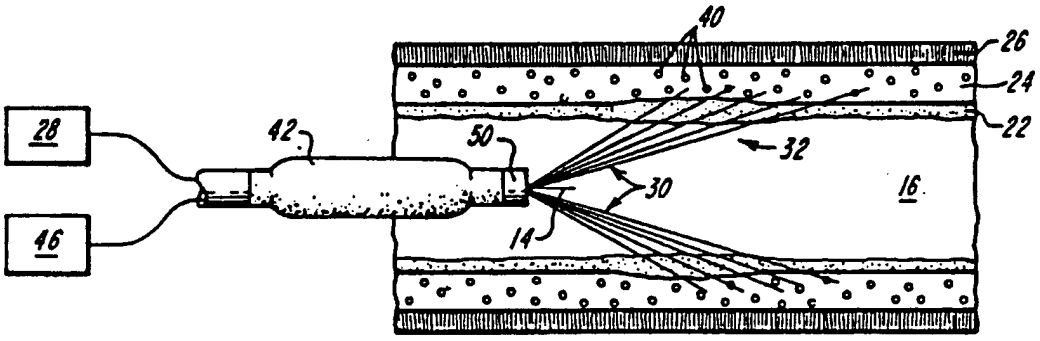

FIG. 3B

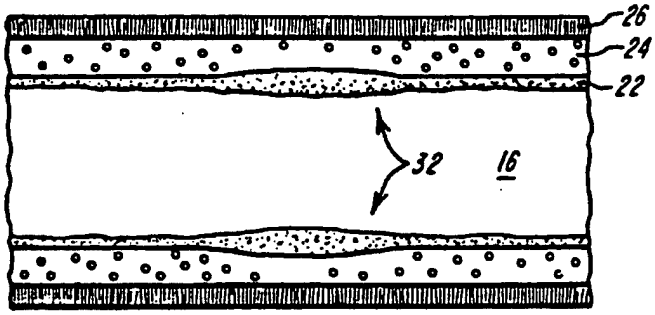

FIG. 3C

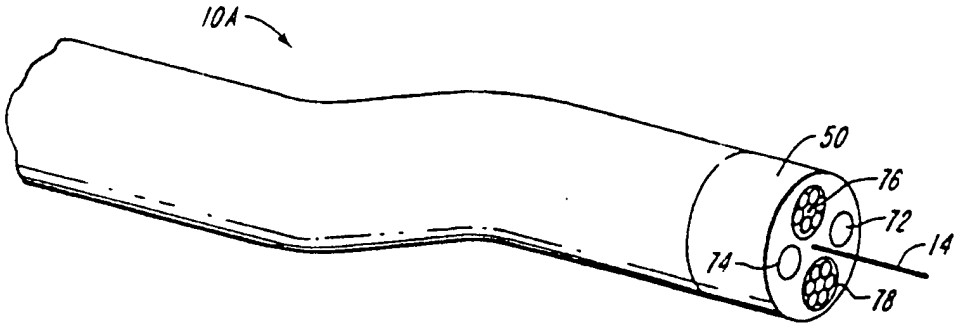

FIG. 4

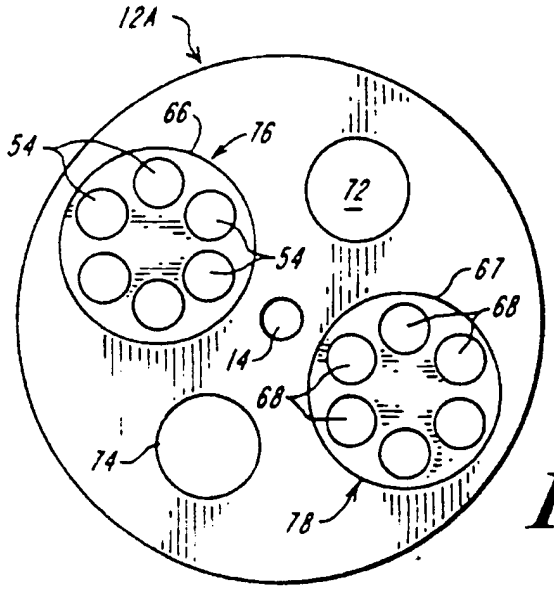

FIG. 5

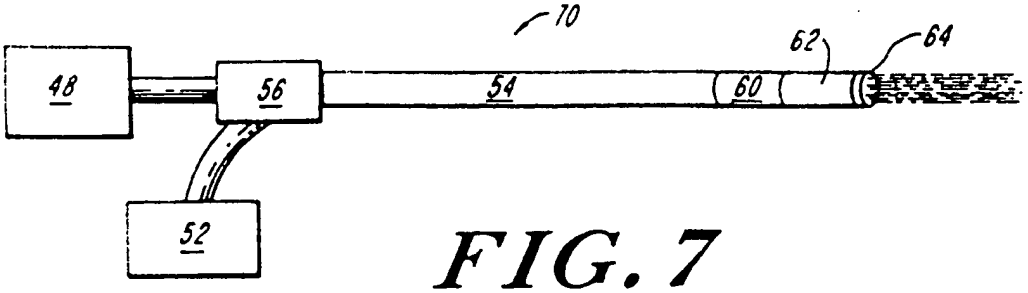

FIG. 7

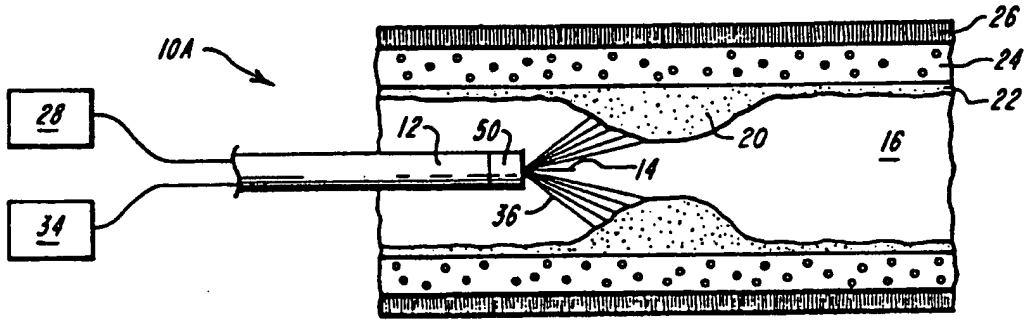

FIG. 6A

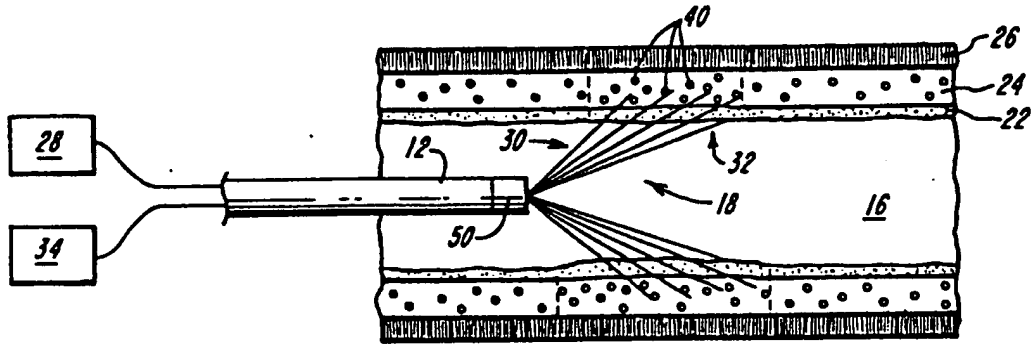

FIG. 6B

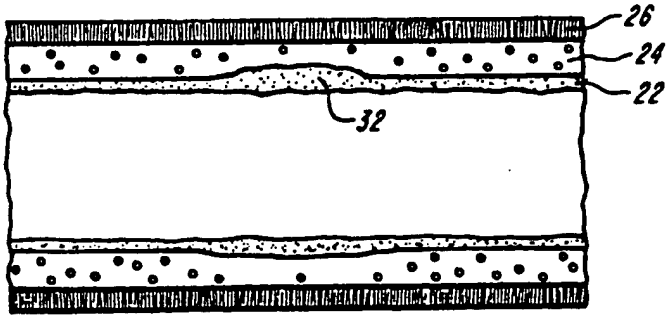

FIG. 6C

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 94 11 0276

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
Y,D	EP-A-0 341 943 (EASTMAN KODAK CO) * column 5, line 29 - line 34 *	1-8	A61B17/22 A61N5/06
Y,D	EP-A-0 182 689 (MEDICAL LASER RESEARCH AND DEVELOPMENT) * page 15, line 22 - line 32 * * page 16, line 2 - line 8; figure 2 *	1-8	
A	EP-A-0 111 060 (IBM) * page 14, line 3 - line 7 *	1	
A,D	EP-A-0 152 766 (SHILEY INC.) * claim 6 *	1	
A	EP-A-0 311 458 (BARD) * claim 1 *	1,7	
A	US-A-4 854 315 (STACK ET AL.) * claim 12 *	1,8	
A	COLOR RESEARCH AND APPLICATION, vol.9, no.4, 1984, NEW YORK pages 195 - 205 P.K.KAISER 'PHOTOTHERAPY USING CHROMATIC, WHITE, AND ULTRAVIOLET LIGHT'		TECHNICAL FIELDS SEARCHED (Int.Cl.5) A61B A61N

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	20 September 1994	Glas, J

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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E : earlier patent document, but published on, or after the filing date
D : document cited in the application
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& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

(19) Europäisches Patentamt
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(54) Inhibition of restenosis by ultraviolet radiation

Restenoseverhinderung durch ultraviolette Bestrahlung

Inhibition de resténose par rayonnement ultraviolet

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(73) Proprietor: **ANGIOMEDICS II, INC.**
Plymouth, MN 55441 (US)

(72) Inventor: **Clarke, Richard H.**
Scituate, MA 02066 (US)

(74) Representative:
Strehl Schübel-Hopf & Partner
Maximilianstrasse 54
80538 München (DE)

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EP-A- 0 341 943
US-A- 4 854 315

- **COLOR RESEARCH AND APPLICATION, vol.9, no.4, 1984, NEW YORK pages 195 - 205 P.K.KAISER 'PHOTOTHERAPY USING CHROMATIC, WHITE, AND ULTRAVIOLET LIGHT'**

EP 0 629 380 B1

Description

Background of the Invention

The technical field of this invention is surgical instruments and, in particular, systems for inhibiting restenosis associated with angioplasty.

Atherosclerosis is a disease which causes thickening and hardening of the arteries, characterized by lesions of raised fibrous plaque formed within the arterial lumen. Atherosclerotic plaque is commonly treated by means of angioplasty through the use of a balloon catheter. Balloon angioplasty involves passing a small, balloon-tipped catheter percutaneously into an artery and up to the region of obstruction. The balloon is then inflated to dilate the area of obstruction. Other devices, such as atherosclerectomy instruments which remove obstructions by peeling or shaving plaque from the artery wall, are also utilized in the treatment of atherosclerosis. More recently, laser systems have been proposed for performing angioplasty. In laser angioplasty, a catheter carrying a fiber optic waveguide is passed through a blood vessel, positioned near an obstruction, and then activated to decompose the plaque with laser radiation.

At present, over 200,000 angioplasty procedures are performed each year in the United States. Unfortunately, restenosis, or closure of the blood vessel following angioplasty, is a common occurrence following all types of such surgery. Approximately 30% of segments dilated by means of balloon catheter will develop significant restenosis, with peak incidence occurring between 2 and 3 months after angioplasty. Similar restenosis rates accompany laser angioplasty. When restenosis occurs, further coronary difficulties can result including strokes, arrhythmia, infarcts and even death.

Evidence suggests that intimal hyperplasia or proliferation of smooth muscle cells is a major factor in restenosis. Proliferation of smooth muscle cells is very common in patients after angioplasty, whether or not restenosis occurs. Medial smooth muscle cells, a main component of the arterial wall, proliferate in response to any injury to the arterial wall. Smooth muscle cells enter their growth cycle between 2 and 3 days after injury, and the majority of smooth muscle cells will cease to proliferate within 7 days. The total number of smooth muscle cells in the intima reaches a peak about two weeks after injury and remains constant for up to one year, suggesting that a reduction of the number of smooth muscle cells injured during angioplasty will reduce the likelihood of subsequent restenosis. See, generally, Liu et al., "Restenosis After Coronary Angioplasty, Potential Biologic Determinants and Role of Intimal Hyperplasia," Vol. 79, Circulation, pp. 1374-1387 (1989).

At present, efforts to prevent restenosis typically consists of drug therapy or modification of angioplasty techniques. Drug therapy is primarily directed toward the control of restenosis through the use of antiplatelet agents, antiproliferative agents, or antimigratory agents. The goal of drug therapy is to reduce smooth muscle cell proliferation by attacking the smooth muscle cells directly, or by affecting processes that promote smooth muscle cell proliferation. Unfortunately, most of the drugs under investigation are unproven, with unknown efficiency and side effects.

An alternative approach to reduce restenosis is to modify the techniques used in performing angioplasty. Until recently, angioplasty was performed by passing a small, balloon-tipped catheter percutaneously to an obstruction site and then inflating the balloon to dilate the area of obstruction. In balloon angioplasty, the outward compression of the balloon stresses the vessel walls, often resulting in cracking or tearing of the wall and injury to the smooth muscle cells. This injury, in turn, increases the risk of restenosis. One method to reduce restenosis resulting from balloon angioplasty is to heat the balloon during dilation to "seal" the injured vessel wall. See, for example, U.S. Pat. No. 4,754,752 issued to Ginsberg et al. on July 5, 1988; and European Patent Application Pub. No. A-0 182 689 published 28 May 1986.

European Patent Application Pub. No. 0 311 458 published 12 April 1889 discloses a laser balloon catheter having an optical fibre for carrying high energy thermal laser radiation which heats tissue surrounding the balloon so that plague-ridden tissue is fused to the artery walls.

Modified forms of laser angioplasty have also been proposed to remove atherosclerotic obstructions. Up until recently, researchers in laser angioplasty primarily have relied upon continuous wave (CW) lasers. Such lasers, while sufficient to ablate an obstruction, can also substantially cause thermal injury to vessel walls adjacent to the obstruction. Recently, high energy excimer lasers and other pulsed laser sources, which possess high peak intensity levels and very rapid pulse rates, have been found to destroy the target obstruction while minimizing the thermal injury to surrounding tissue. See, for example, European Patent Application Pub. No. A-0 152 766.

A device according to the preamble of claim 1 is known from EP-A-0 341 943. This document relates to a vascular catheter. The catheter includes a cutting device to remove obstructions and a low power laser that delivers no more than about 500mW of power at wavelengths from about 600 to 1000nm for preventing restenosis. The low power laser light is effective to devitalize and seal the fresh vessel surface exposed by the cutting device. Lasing of these tissues acts on medial smooth muscle cells of the vessel wall and destroys them by heat. Thereby the vessel walls are sealed, or thermally coagulated, which retards the proliferation.

Nonetheless, even with these less traumatic procedures, restenosis continues to be a significant factor compromising the effectiveness of angioplasty.

There exists a need for better methods and devices for preventing restenosis after angioplasty. A system which

could perform angioplasty, while reducing the likelihood of smooth muscle cell proliferation in the vicinity of the angioplasty site, would satisfy a significant need in the art.

Summary of the Invention

Restenosis following angioplasty can be inhibited by reducing the proliferation of smooth muscle cells in the blood vessel walls at an angioplasty site, and such reduction in cell proliferation can be accomplished by irradiating the angioplasty site with the appropriate radiation in the ultraviolet (UV) wavelength range. The ultraviolet radiation is preferably delivered via an optical fiber or other waveguide incorporated, for example, into a percutaneous catheter. In operation, the ultraviolet radiation kills smooth muscle cells at the site, thereby reducing the risk of restenosis, while minimizing damage to surrounding tissue.

Various UV radiation sources can be used in accordance with the present invention to deliver restenosis-preventive therapy, including both laser and non-coherent radiation sources. Either pulsed or continuous wave ("CW") lasers can be used, and the lasant medium can be gaseous, liquid or solid state. One preferred laser source is a pulsed excimer laser, such as a KrF laser. Alternatively, rare earth-doped solid state lasers, ruby lasers and Nd:YAG lasers can be operated in conjunction with frequency modification means to produce an output beam at the appropriate UV wavelength In another alternative, a UV flash lamp can be employed.

The UV radiation source produces an output beam having a wavelength less than about 280 nanometers. The therapeutic UV radiation useful in the present invention ranges from 280 nanometers down to 240 nanometers (due to the limited transmission efficiency of glass fibers at lower wavelengths). In one preferred embodiment, a laser system is disclosed which operates at about 266 nanometers to maximize the cytotoxic effect of the radiation. Other useful UV radiation sources include, for example, Argon ion lasers emitting UV light at about 257 nanometers and KrF excimer lasers emitting light at about 248 nanometers.

The invention can be practiced with a low energy radiation source. The term "low energy" is used herein to describe both laser and non-coherent radiation systems having an energy output of less than 5 millijoules per pulse.

The term "high energy" is used herein to describe lasers which have an energy output of more than 5 millijoules per pulse or which generate peak powers on the order of 100 kilowatts per square centimeter or greater.

In one embodiment of the invention, at least one optical fiber for transmission of UV radiation is incorporated into a conventional balloon angioplasty device and operated to deliver therapeutical UV radiation to the angioplasty site either at the same time the balloon is inflated, or shortly before or after inflation. In one preferred method, the balloon is first inflated to displace the vessel-obstructing plaque or lesion, and then the balloon is retracted to permit irradiation of the site by one of the optical waveguides incorporated into the catheter. In one illustrated embodiment, the balloon catheter has a diffusive tip through which the therapeutic UV laser radiation of the invention is delivered.

In another embodiment of the invention, at least one optical waveguide for transmission of UV radiation can be incorporated into an laser angioplasty device as an adjunct to the delivery of ablative laser radiation. Thus, a single catheter preferably can carry two bundles of optical fibers, one bundle serving to deliver ablative radiation (e.g., from a high energy, pulsed, excimer laser) and the other bundle carrying the UV radiation to kill a portion of the cells in the vicinity of the ablation site which would otherwise proliferate.

In this embodiment, the ablative and therapeutic radiation can be provided by two or more lasers operating in tandem, one laser source being used to deliver ablative laser radiation, and another laser source then employed to inhibit restenosis. In one preferred embodiment, separate optical waveguides can be used to deliver the ablative and therapeutic laser radiation, and two controllers are provided, one for each laser source, to allow them to operate independently. Alternatively, the ablative and therapeutic radiation can multiplexed and delivered via the same waveguide The ablative laser radiation source can be any form of laser deemed appropriate for the particular application involved. In another alternative, a tunable laser delivering radiation at two or more wavelengths can be used and may be preferred for particular applications.

In another aspect of the invention, novel UV radiation sources are disclosed herein which overcome the problems of low transmissivity and low damage thresholds in fused silica or glass fibers by doping the fiber with a lasant such as Neodymium. The optical fiber is then pumped by energy from an optical pump source and acts as an amplifier to produce a full strength laser output beam at its distal end. High intensity pulsed radiation can be achieved by introducing a low power laser pulse into the proximal end of the fiber. Short wavelength visible and/or ultraviolet radiation can be obtained by disposing one or more frequency-modifying elements at the distal end of the instrument.

In one illustrated embodiment, a laser having an output beam wavelength of about 1064 nanometers, such as a common Nd:YAG laser, can be used in conjunction with two doubling crystals to yield a radiation output of about 266 nanometers. A grouping of six to eight fibers delivering such radiation can be used to provide the laser power necessary for both ablation of plaque and treatment of the site to reduce the likelihood of restenosis.

Novel catheter systems are also disclosed herein. Such catheter systems are useful in the performance of either balloon angioplasty or laser angioplasty and are preferably equipped with at least one optical waveguide for delivery of

the UV radiation therapy, which can be, for example, an optical fiber having about a 200 micron diameter core. The catheter tip can also contain focusing optics or diffusive elements for use in directing the radiation emitted from the catheter within an artery.

Brief Description of the Drawings

FIG. 1 is a schematic perspective view of a combined balloon and laser therapy catheter for performing angioplasty and reducing the likelihood of restenosis;

FIG. 2 is a view of the distal end of the catheter of FIG. 1;

FIGS. 3A-3C are schematic cross-sectional illustrations of a system incorporating the catheter of FIG. 1 in use to dilate a blood vessel and prevent restenosis;

FIG. 4 is a schematic perspective view of an alternative catheter for performing angioplasty and reducing the likelihood of restenosis;

FIG. 5 is a view of the distal end of the catheter of FIG. 4;

FIGS. 6A-6C are schematic cross-sectional illustrations of a system incorporating the catheter of FIG. 4 in use to dilate a blood vessel and prevent restenosis; and

FIG. 7 is a schematic illustration of a laser device useful in the present invention.

Detailed Description

In FIG. 1, a combined balloon and laser therapy catheter 10 is shown, including inflatable balloon section 42 and a guide wire 14. Also disposed within the catheter are a plurality of optical fibers 54 for delivery of ultraviolet radiation. The catheter can also include a radio-opague tip 50. In FIG. 2, the distal end 12 of the catheter of FIG. 1 is shown in more detail, including an exemplary disposition of six optical fibers 54 about a central guide wire 14.

The use of the catheter system 10 is schematically illustrated in FIGS. 3A-3C. In use, the guide wire 14 is first introduced into the obstructed blood vessel and used to guide the catheter 10 into position adjacent to the plaque or lesion (e.g., under radiographic control). As shown in FIG. 3A, the balloon section 42 is then inflated to form a balloon 44 which applies pressure against the obstruction 20, thereby dilating the obstructed region of the blood vessel 16. Inflation and deflation of the balloon 44 are controlled by a balloon controller 46.

In FIG. 3B, the balloon section 42 is deflated and retracted so that the distal tip of the catheter can be positioned to deliver UV radiation therapy to the angioplasty site 32. A therapeutical laser 28 can then be activated to deliver UV radiation 30 which will kill a major portion of the smooth muscle cells 40 within the media 24 of the blood vessel wall without damaging either the inner endothelium layer 22 or the outer adventitia 26 of the blood vessel.

As shown in FIG. 3C, the end result of the operation is a substantially lessened obstruction with few, if any, smooth muscle cells remaining in the angioplasty site to proliferate and cause restenosis.

In FIGS. 4 and 5, an alternative catheter configuration 10A for performing both angioplasty and reducing the likelihood of restenosis is shown, including a guide wire 14 and two laser radiation delivery systems 76 and 78. The first laser delivery system 76 provides therapeutic UV radiation to inhibit restenosis. The second laser delivery system 78 operates to provide ablative laser radiation to remove obstructions in a blood vessel by photodecomposition. Like the system of FIG. 1, the catheter of FIG. 4 can also include a radio-opaque tip 50 to aid in positioning the catheter within a blood vessel under radiographic control.

As shown in more detail in FIG. 5, the distal end of 12A of the catheter can include both the therapeutic UV radiation delivery system 76 and the ablative laser radiation delivery system 78. Multiple optical fibers 54 for UV radiation therapy are encased in a sleeve 66 which is positioned on one side of the guide wire to provide the UV therapy system. A second sleeve 67, encasing another set of optical fibers 68 for laser ablation, is positioned on the other side of the guide wire 14.

The catheter can further include a flushing port 72 for the introduction of saline at the site and/or a suction port 74 for clearing the site of fluids during laser operations. The optical waveguides 68 may be of any type appropriate to deliver the ablative laser radiation required for a particular application. For example, the optical waveguide 68 can be optical fibers connected to an ablative radiation source such as a XeCl excimer laser operating in a pulsed mode at about 308 nanometers.

The use of the catheter system 10A is schematically illustrated in FIGS. 6A-6C. As shown, the catheter and guide

wire can be introduced into a blood vessel 16. The walls of the blood vessels are characterized as having an inner endothelium layer 22, a media populated by smooth muscle cells 24 and an outer adventitia 26. In atherosclerotic disease, the endothelium 22 is interrupted by lesions of raised fibers plaque 20. In use, the catheter 10A is positioned next to the obstruction 20 and the ablative radiation source 38 is activated to provide a radiation beam 36 which removes the plaque by photodecomposition. Next, the therapeutic UV radiation source 28 is activated to provide a second beam of radiation 30 which is directed to the smooth muscle cells 40 within the blood vessel media 28 at the angioplasty site 32.

Following the therapeutic UV radiation, the catheter can be withdrawn as shown in FIG. 6C, and few smooth muscle cells will remain within the area of the angioplasty injury. By killing a major portion of the smooth muscle cells, the risk of restenosis is again decreased.

As noted above, the therapeutic UV radiation can be provided by a variety of sources, including non-coherent UV light sources and excimer laser sources (e.g., a KrF excimer laser operating at 248 nanometers).

In FIG. 7, an alternative laser device 70 is shown which can be used in the present invention to provide the therapeutic UV radiation. In the system 70, an output beam from a laser source 48, such as Nd:YAG laser with an output radiation having a wavelength of about 1064 nanometers is introduced via coupler 56 into an optical fiber 54 which is preferably a rare earth-doped silica fiber (e.g. a Neodymium-doped optical fiber). As the radiation from laser source 48 is introduced into the optical fiber 54, the fiber is also optically pumped by an optical pump source 52 (e.g., a laser diode having an output radiation wavelength of about 808 nanometers, likewise coupled to the fiber 54 by coupler 56). The doped optical fiber thus acts a laser amplifier.

At the distal end of fiber 54, the system is terminated in two frequency-multiplying crystals 60 and 62. The first crystal 60 is a frequency-doubling optical element, such as a potassium dihydrogen phosphate (KDP) crystal, and the second crystal 62 is also a frequency-doubling optical element, such as a barium boron oxide (BBO) crystal. Focusing optics 64, such as a grated refractive index ("GRIN") lens, can be included at the output end of the optical fiber 54. With the system as described, laser radiation of a wavelength of about 266 nanometers is produced.

In the laser device 70 of Fig. 7, the pulsed Nd:YAG laser is chosen for its capability to operate as a rapidly pulsed laser and for its availability at low cost. In particular applications it may be preferred to employ pulsed energy sources other than a Nd:YAG laser. The pulsed laser medium can be gaseous, liquid or solid-state. Rare earth-doped solid state lasers, ruby lasers, alexandrite lasers, carbon dioxide lasers and excimer lasers are all examples of lasers that can be operated in pulsed mode and used as pulse-triggering elements in the present invention.

The laser device 70 is particularly adapted for use within a catheter. In one embodiment, a plurality of optical fibers of the type described herein can be used to provide the needed energy for performing either laser surgery or restenosis preventive therapy. The laser surgical systems of the present invention preferably have an output energy ranging from about 50 to to about 100 millijoules per pulse. For a non-ablative, therapeutic application, the systems can be operated at lower output energies, for example, from about 100 microjoules to about 10 millijoules. Other output energies can be employed as needed for particular applications. Likewise, the number of delivery fibers can be varied to adjust the total system output. Moreover, the laser device of Fig. 7 can be incorporated into other surgical tools, such as laser scalpels and/or endoscopes.

The utility of UV radiation in reducing the proliferation of vascular smooth muscle cells has been further demonstrated by experiments In one set of experiments using cultured cells, the A10 rat embryonic thoracic aorta cell line was obtained from the American Type Culture Collection. This clonal, smooth muscle line was derived from the thoracic aorta of DD1X embryonic rats. The cells possess many of the characteristics of end-stage smooth muscle cells; they produce spontaneous action potential at the stationery phase of growth and exhibit an increase in activity of the enzymes mykinase and creatine phosphokinase.

The cell line was propagated in DMEM medium supplemented with 10% fetal bovine serum and glutamine. These cells were plated on well tissue culture plates. After incubation for three to four days, cells in expotential growth were irradiated using laser radiation of various wavelengths. All of the experiments were run at a laser repetition rate of 10 Hz. The area of cell wall exposed was approximately 9.62 cm^2. The results are detailed in Table 1 below.

TABLE 1

Results of Laser Irradiation of Smooth Muscle Cells			
Laser Wavelength	Energy/Pulse	Exposure Time	Surviving Fraction
control	--	--	1.05
control	--	--	0.95
266 nm	10 mj	1 min	0.00916
266 nm	9.6 mj	15 sec	0.0358

TABLE 1 (continued)

Results of Laser Irradiation of Smooth Muscle Cells			
Laser Wavelength	Energy/Pulse	Exposure Time	Surviving Fraction
266 nm	9.9-1.1 mj	1 min	0.114
355 nm	10.2 mj	1 min	1.12
1064 nm	>10 mj	1 min	1.03
266+532+1064	>10 mj	1 min	<0.001
532+1064	>10 mj	1 min	1.08

These results clearly demonstrate the efficacy of UV radiation in killing aortic smooth muscle cells. Cell cultures exposed to as little as 15 seconds of UV radiation exhibited survival rates below 1 percent.

Claims

1. A phototherapeutic apparatus comprising a catheter (10) adapted for insertion inside a blood vessel (16) and location adjacent to a treatment site within the vessel, and irradiation means disposed within the catheter (10) for irradiating the treatment site (32) to prevent restenosis, the irradiation means emitting non-ablative radiation with an energy level sufficient to kill a portion of smooth muscle cells (40) forming the blood vessel (16) in the vicinity of the treatment site,

   characterised in that the irradiation means delivers low-power UV radiation having a wavelength ranging from 240 to 280 nm, and delivers such therapeutical radiation to the treatment site without ablation lesions or damage to the surrounding tissue of the blood vessel, thereby reducing susceptibility to restenosis due to blood vessel cell proliferation.

2. The apparatus of claim 1 wherein the irradiation means further includes an optical diffuser at the distal end to diffuse the radiation.

3. The apparatus of claim 1 wherein the irradiation means further includes a low power laser (28) emitting UV radiation.

4. The apparatus of claim 3 wherein the laser (28) delivers a radiation beam having a wavelength of about 248 to about 268 nm.

5. The apparatus of claim 1 wherein the irradiation means further includes a UV flash lamp emitting UV radiation.

6. The apparatus of claim 3, 4 or 5 wherein the irradiation means further comprises at least one optical waveguide (76) disposed within the catheter (10) .

7. The apparatus of any preceding claim wherein the irradiation means includes a pulsed radiation source.

8. The apparatus of claim 7 wherein the radiation source is a pulsed laser having an energy level below 5 mJ per pulse.

9. The apparatus of claim 8 wherein the pulsed laser is an Argon ion laser or an excimer laser.

10. The apparatus of any of claims 1 to 6 wherein the irradiation means includes a continuous wave radiation source.

11. The apparatus of claim 10 wherein the radiation source is a laser emitting continuous wave radiation and having a peak power less than 100 kW/cm^2.

12. The apparatus of claim 10 wherein the irradiation means is a rare-earth doped solid-state laser, preferably a Nd:YAG laser.

13. The apparatus of any of claims 10 to 12 wherein the irradiation means further includes a frequency modifying

means.

Patentansprüche

1. Phototherapeutisches Gerät mit einem zum Einsetzen in ein Blutgefäß (16) und Anordnen nahe einer Behandlungsstelle in dem Gefäß geeigneten Katheter (10) und einer innerhalb des Katheters (10) angeordneten Bestrahlungseinrichtung zum Bestrahlen der Behandlungsstelle (32) zur Verhütung von Restinose, wobei die Bestrahlungseinrichtung nicht-abtragende Strahlung eines Energiepegels aussendet, der ausreicht, um einen Teil der das Blutgefäß (10) bildenden glatten Muskelzellen (40) in der Umgebung der Behandlungsstelle abzutöten,
   dadurch **gekennzeichnet**, daß die Bestrahlungseinrichtung energiearme UV-Strahlung mit einer Wellenlänge im Bereich von 240 bis 280 nm abgibt und diese therapeutische Bestrahlung der Behandlungsstelle ohne Abtragungs-Verletzung oder Beschädigung des umgebenden Blutgefäßgewebes zuführt und dadurch Restinoseanfälligkeit aufgrund von Zellenwucherung des Blutgefäßes verringert.

2. Gerät nach Anspruch 1, wobei die Bestrahlungseinrichtung ferner am distalen Ende ein optisches Streuelement zur Streuung der Strahlung aufweist.

3. Gerät nach Anspruch 1, wobei die Bestrahlungseinrichtung ferner einen UV-Strahlung emittierenden Laser (28) niedriger Leistung aufweist.

4. Gerät nach Anspruch 3, wobei der Laser (28) Strahlung mit einer Wellenlänge von etwa 248 bis etwa 268 nm abgibt.

5. Gerät nach Anspruch 1, wobei die Bestrahlungseinrichtung ferner eine UV-Strahlung emittierende UV-Blitzlichtlampe aufweist.

6. Gerät nach Anspruch 3, 4 oder 5, wobei die Bestrahlungseinrichtung ferner mindestens einen in dem Katheter (10) angeordneten optischen Wellenleiter (76) aufweist.

7. Gerät nach einem der vorhergehenden Ansprüche, wobei die Bestrahlungseinrichtung eine gepulste Strahlungsquelle enthält.

8. Gerät nach Anspruch 7, wobei die Strahlungsquelle ein gepulster Laser mit einem Energieniveau unter 5 mJ pro Puls ist.

9. Gerät nach Anspruch 8, wobei der gepulste Laser ein Argonionen- oder ein Excimer-Laser ist.

10. Gerät nach einem der Ansprüche 1 bis 6, wobei die Bestrahlungseinrichtung eine Strahlungsquelle mit kontinuierlicher Welle ist.

11. Gerät nach Anspruch 10, wobei die Strahlungsquelle ein Strahlung mit kontinuierlicher Welle emittierender Laser mit einer Spitzenleistung unter 100 kW/cm^2 ist.

12. Gerät nach Anspruch 10, wobei die Bestrahlungseinrichtung ein mit einer seltenen Erde dotierter Festkörperlaser, vorzugsweise ein Nd:YAG-Laser, ist.

13. Gerät nach einem der Ansprüche 10 bis 12, wobei die Bestrahlungseinrichtung ferner eine Frequenz-Modifiziereinrichtung aufweist.

Revendications

1. Appareil photothérapeutique, comprenant un cathéter (10) adapté pour être inséré à l'intérieur d'un vaisseau sanguin (16) et situé de façon adjacente à un site de traitement à l'intérieur du vaisseau, et des moyens d'irradiation disposés à l'intérieur du cathéter (10) pour irradier le site de traitement (32) pour éviter la resténose, les moyens d'irradiation émettant un rayonnement non ablatif ayant un niveau d'énergie suffisant pour tuer une partie des cellules de muscle lisse (40) formant le vaisseau sanguin (16) au voisinage du site de traitement,
   caractérisé en ce que les moyens d'irradiation émettent un rayonnement ultraviolet de faible puissance ayant une longueur d'onde dans la plage entre 240 et 280 mm, et délivrent un tel rayonnement thérapeutique au site de trai-

tement sans lésions d'ablation ou endommagement du tissu environnant du vaisseau sanguin, en réduisant ainsi la possibilité de resténose du fait de la prolifération des cellules du vaisseau sanguin.

2. Appareil selon la revendication 1, dans lequel les moyens d'irradiation comprennent de plus un diffuseur optique à l'extrémité distale pour diffuser le rayonnement.

3. Appareil selon la revendication 1, dans lequel les moyens d'irradiation comportent de plus un laser à faible puissance (28) émettant un rayonnement ultraviolet.

4. Appareil selon la revendication 3, dans lequel le laser (28) délivre un rayonnement ayant une longueur d'onde d'environ 248 à environ 268 nm.

5. Appareil selon la revendication 1, dans lequel les moyens d'irradiation comportent de plus une lampe à flash ultraviolet émettant un rayonnement ultraviolet.

6. Appareil selon la revendication 3, 4 ou 5, dans lequel les moyens d'irradiation comportent de plus au moins un guide d'onde optique (76) disposé à l'intérieur du cathéter (10).

7. Appareil selon l'une quelconque des revendications précédentes, dans lequel les moyens d'irradiation incluent une source de rayonnement pulsé.

8. Appareil selon la revendication 7, dans lequel la source de rayonnement est un laser pulsé ayant un niveau d'énergie inférieur à 5 mJ par impulsion.

9. Appareil selon la revendication 8, dans lequel le laser pulsé est un laser à ions argon ou un laser excimère.

10. Appareil selon une quelconque des revendications 1 à 6, dans lequel les moyens d'irradiation incluent une source de rayonnement d'onde continue.

11. Appareil selon la revendication 10, dans lequel la source de rayonnement est un laser émettant un rayonnement d'onde continue et ayant une puissance de crête inférieure à 100 kW/cm^2

12. Appareil selon la revendication 10, dans lequel les moyens d'irradiation sont un laser à l'état solide dopé par une terre rare, de préférence un laser Nd :YAG.

13. Appareil selon une quelconque des revendications 10 à 12, dans lequel les moyens d'irradiation comportent de plus des moyens de modification de fréquence.

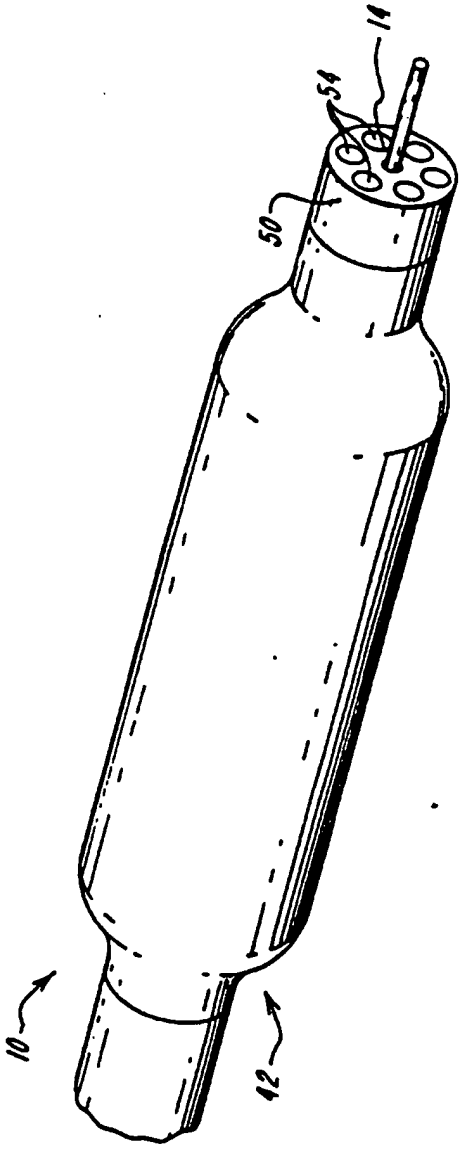

FIG. 1

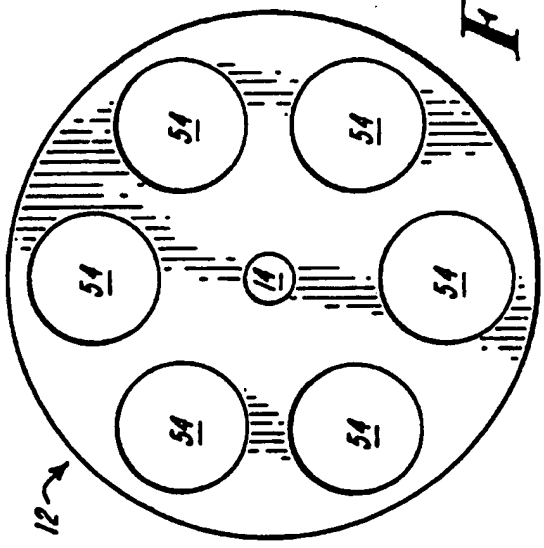

FIG. 2

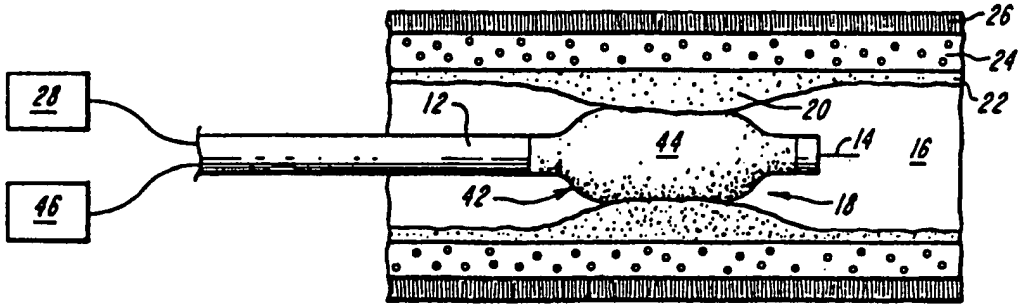

FIG. 3A

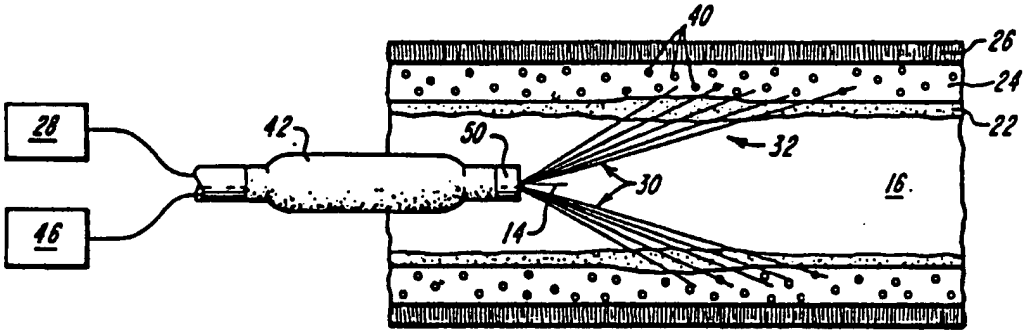

FIG. 3B

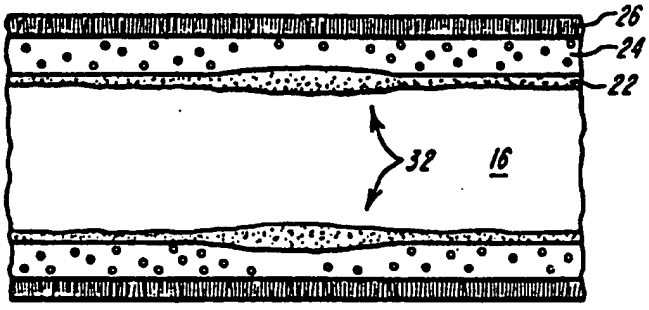

FIG. 3C

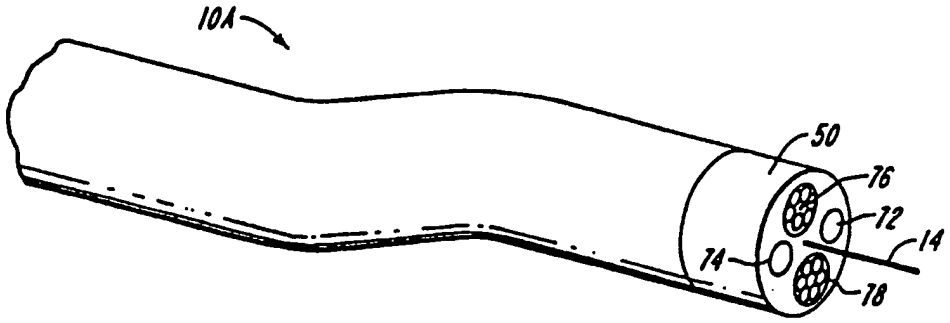

FIG. 4

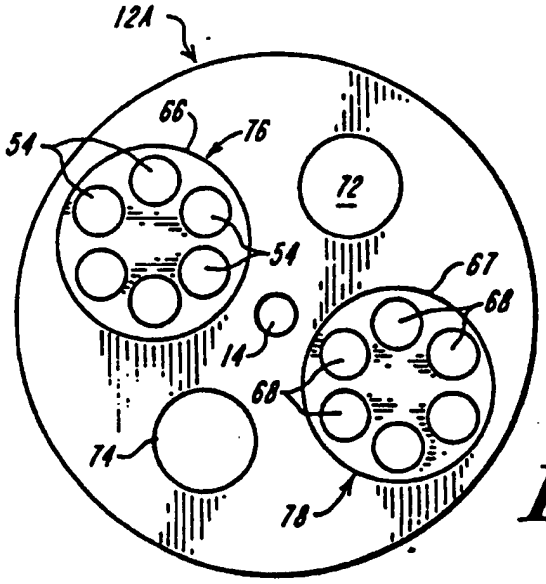

FIG. 5

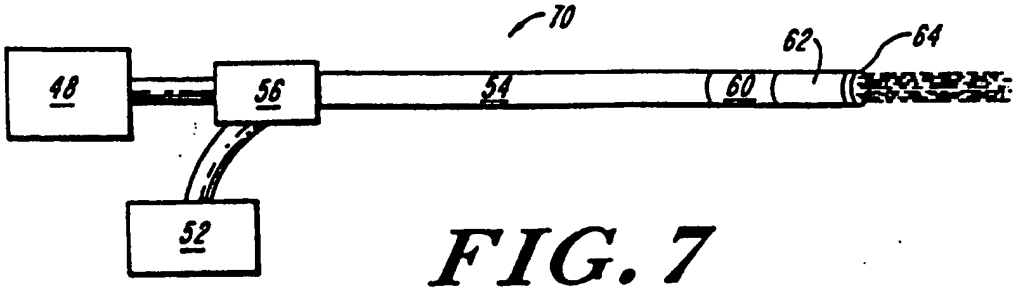

FIG. 7

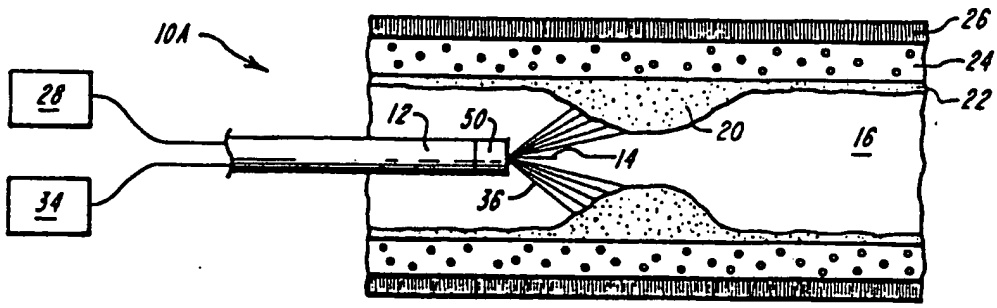

FIG. 6A

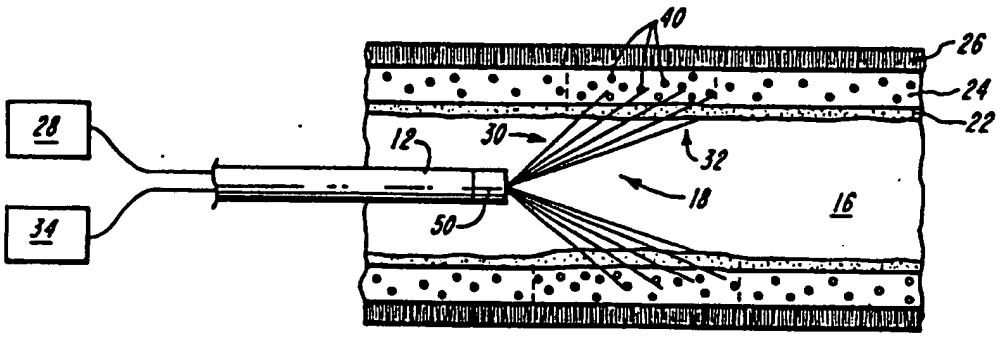

FIG. 6B

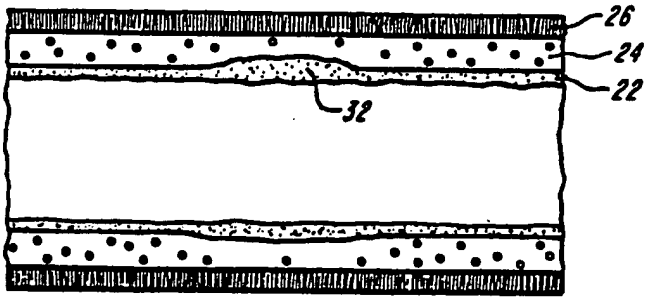

FIG. 6C